Marcello Crucianelli,
Francesco De Angelis
Dipartimento di Chimica,
Ingegneria Chimica e Materiali
Università dell'Aquila
cruciane@univaq.it
Raffaele Saladino
Dipartimento di Agrobiologia ed Agrochimica
Università della Tuscia
saladino@unitus.it

IMMOBILIZATION OF MTO

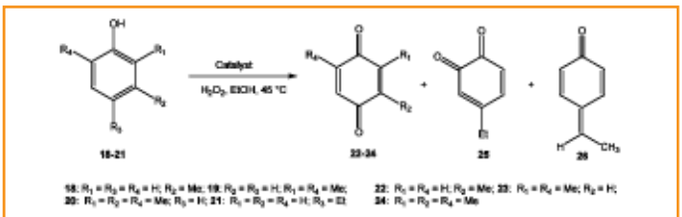
Part 2: A way to enhance oxidative catalysts versatility

From an academic and industrial point of view, the interest in the development of environment friendly heterogeneous catalytic processes gained recently an ever increasing importance. The results obtained in the last five years, in the selective oxidative functionalization of many different organic substrates by means of the novel polymer supported methyltrioxorhenium/H_2O_2 catalytic systems, are presented.

Selective oxidation of natural phenol, polyphenol and anisole derivatives

Poly(4-vinylpyridine) or poly(4-vinylpyridine-*N*-oxide)/MTO systems, 2% or 25% cross-linked with divinylbenzene I-III, acted as efficient and selective catalysts for the conversion of alkyl-substituted phenols to the corresponding benzoquinones, using H_2O_2 as the oxygen donor [1]. All catalysts were stable systems for at least five recycling experiments. In the case of *para*-unsubstituted phenols with small alkyl side-chains 18-20, the corresponding *para*-benzoquinones 22-24 were selectively obtained in high yields (70-90% based on converted starting material), by using PVP-2%/MTO system I as the most active catalyst (Scheme 1). With the *para*-substituted phenol 21 a different selectivity was observed, and the *ortho*-benzoquinone 25 became the main reaction product, along with the quinone methide derivative 26. When the poly(4-vinylpyridine)/MTO catalysts were applied for the oxidation of natural *para*-unsubstituted phenols with a longer alkyl side-chain obtained from cardanol, such as compounds 27 and 28, the regioselectivity of the reaction was

Devoted to prof. Elio Santacesaria in honour of his 65th birthday and of his constant contribution to innovative new processes development in industrial chemistry.



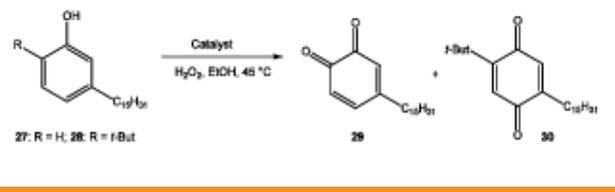
Scheme 1 - Catalytic oxidation of natural phenols 18-21

found to be dependent on the nature and the position of the substituents (Scheme 2).

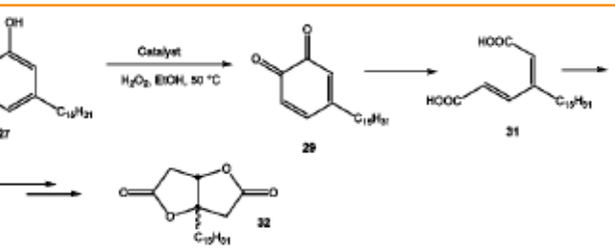
In particular, the presence of an alkyl substituent on the C-2 position of the phenolic ring, as in substrate 28, appears to direct the selectivity of the oxidation from orthobenzoquinone 29 to *para*-benzoquinone 30. The suggestion that PVP/MTO catalysts may organize the cardanol substrates on the surface of their particles, by means of specific and selective molecular recognition processes, is at least in part confirmed by the higher conversions and yields to corresponding benzoquinones, observed in comparison with MTO in homogeneous phase.

The polymer supported MTO oxidations of anisoles behave in a similar way to give benzoquinones as the main reaction products through demethoxylation processes.

In the oxidation of hydrogenated cardanol 27, microencapsulated MTO catalyst V shows a different selectivity with respect to previously described PVP/MTO systems, affording the di-γ-lactone



Scheme 2 - Catalytic oxidation of natural phenols 27-28



Scheme 3 - Oxidation of cardanol derivative 27 by catalyst V

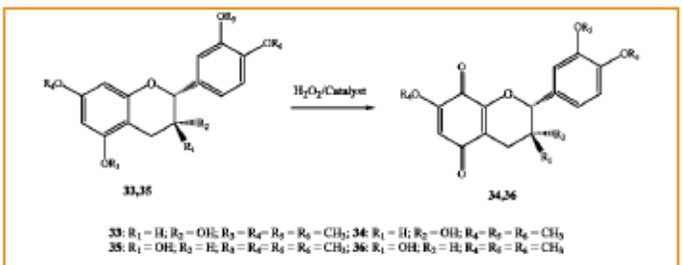
derivative 32 as the main reaction product (Scheme 3). This latter compound is formed by oxidative ring-opening of the firstly formed ortho-quinone 29, to give the muconic acid 31, followed by a tandem intramolecular Michael addition [2].

Di-γ-lactones similar to 32 exhibit a wide range of biological activities, such as allergenic, antitumor, antimicotic, antimicrobial and antiviral properties.

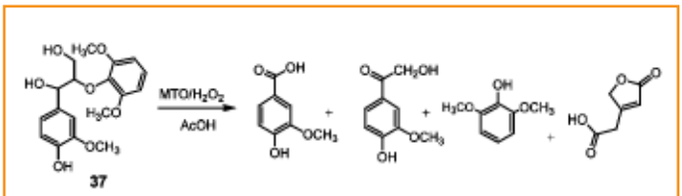
The same MTO polymer-supported/H_2O_2 catalytic systems worked well in the selective oxidation of catechin and epicatechin derivatives 33 and 35, to *para*-benzoquinones 34 and 36 respectively, in acetic acid (Scheme 4) [3]. Better results were obtained working with the PVP-25%/MTO catalyst II, evidencing the influence of morphologic properties of the polymeric support on the efficiency of the catalyst.

The high efficacy showed by polymer supported MTO catalysts in the oxidation of phenols and anisole derivatives has been successively applied to the development of environmental friendly pulping and bleaching processes in the paper production industry, avoiding the use of chlorinated compounds [4]. The major drawback of these processes consists in a lack of selectivity in the oxidation of lignin, which leads to the partial degradation of the cellulose contained in pulps, and ultimately in a lower final product yield. The lack of selectivity is due fundamentally to the formation of radical intermediates, such as hydroxyl radicals, that are able to attack both cellulose and lignin. Selective catalytic processes based on a concerted oxygen atom transfer from environmental friendly MTO/H_2O_2 might solve these problems. In order to evaluate this selectivity, a selected array of monomeric and dimeric lignin model compounds resembling the main bonding patterns in native and technical lignins, has been oxidized with supported MTO catalysts in the presence of H_2O_2. As for example the oxidation of compound 37, that represents the most abundant bonding pattern in softwood and hardwood lignins, is reported in Scheme 5 [5].

The heterogeneous catalytic systems based on H_2O_2/and MTO catalysts I-III and V are able to extensively oxidize both phenolic and non-phenolic, monomeric, and dimeric lignin model compounds without the presence of phenoxy radical coupling. In all examined cases the cleavage of the alkyl side chain, or both alkyl side-chain



Scheme 4 - Catalytic oxidation of catechin and epicatech in derivatives 33 and 35

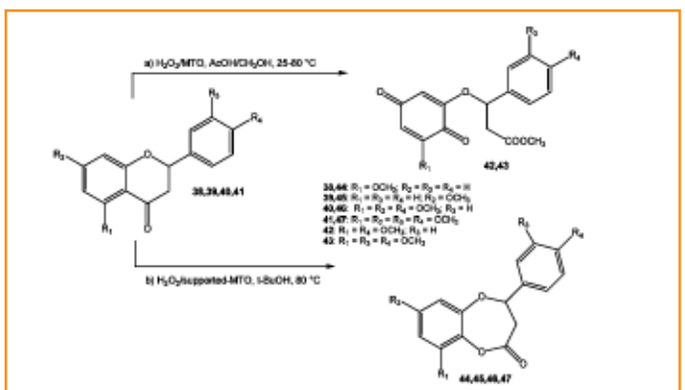


Scheme 5 - Catalytic oxidation of lignin model compound 37

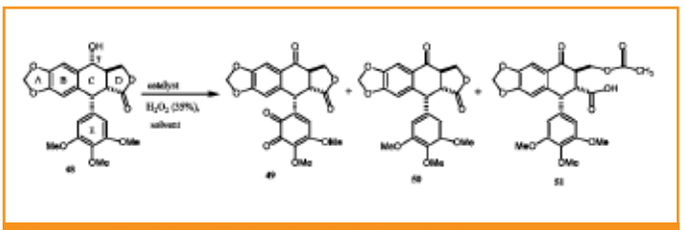
oxidation and aromatic ring cleavage were the operative processes. Recalcitrant diphenylmethane units were also efficiently degraded.
Some considerations can be drawn about the catalytic behavior of catalysts I-III and V depending on their structural properties. In this context, two main parameters appear of great relevance for the lignin model compound oxidations with poly(4-vinylpyridine) based catalysts: the reticulation grade of the resin and the oxidation state of the pyridinyl moieties (*i.e.*, pyridine *vs* pyridine *N*-oxide as anchorage site for the rhenium atom). Technical lignins, such as hydrolytic sugar cane lignin (SCL) and red spruce kraft lignin (RSL), were also efficiently degraded by immobilized catalytic systems I-III and V.

Baeyer-Villiger rearrangement of flavonone derivatives

Naturally occurring flavonoids such as naringenin 40 and hesperetin 41 were selectively oxidized to the corresponding lactones 46 and 47 with high conversions of substrates and satisfactory yields, by H_2O_2 activated by poly(4-vinylpyridine) or poly(4-vinylpyridine-*N*-oxide)/MTO systems I-IV, in *tert*-butanol (Scheme 6, pathway b) [6]. By the same way the 5-methoxyflavanone 38 and 7-methoxy flavanone 39 gave respectively lactones 44 and 45. Differently from what observed working with MTO/H_2O_2 system in homogeneous acidic conditions, in this case no formation of quinone derivatives 42 and 43 occurred at all (Scheme 6, pathway a), as a consequence of the known tuned activity showed by MTO when complexed with a good ligand as pyridine.



Scheme 6 - Catalytic oxidation of flavonoids 38-41



Scheme 7 - Catalytic oxidation of podophyllotoxin 48

Oxidation of lignan derivatives

The versatility of homogeneous or heterogeneous MTO-based oxidants have been recently observed also in the functionalization of an important class of natural product derivatives, such as lignans. Lignans show a broad variety of biological and pharmacological activities. Among them, aryltetralin derivatives are of special interest owing to their powerful antitumoral, antimicotic, antiviral, cardiovascular and immunosuppressive activity.
Few data are available on oxidative functionalization of aryltetralin derivatives, a process that plays a relevant role in their biological mechanism of action. In this context, MTO and heterogeneous polymer supported PVP-2/MTO I and PS/MTO V catalysts have been successfully used in the oxidative derivatization of podophyllotoxin 48, affording, irrespective of experimental conditions used, products deriving from the oxidation of benzylic positions and of aromatic moieties (Scheme 7) [7].
The performance of PVP-2/MTO catalyst I in AcOH at 40 °C was similar to that observed for MTO in mixed solvents (such as CH_2Cl_2/CH_3CN or CH_2Cl_2/EtOH), affording compound 49, that is *ortho*-benzoquinone of isopodophyllotoxone, as the only recovered product in quantitative conversion of substrate and 69% yield. Similar results were obtained in a different solvent such as a 1:1 CH_2Cl_2/EtOH mixture. A different reaction pathway was otherwise observed with PS/MTO V catalyst. In this latter case, the oxidation in AcOH at 25 °C gave the acetylated D-ring opened isopodophyllotoxone derivative 51 as the main reaction product

RIASSUNTO

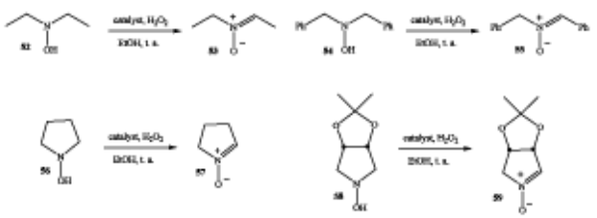
Immobilizzazione del MTO. Una via per aumentare la versatilità dei catalizzatori ossidativi

L'interesse nel settore della ricerca universitaria e dell'industria, verso lo sviluppo di nuove metodologie catalitiche in fase eterogenea ecocompatibili, ha visto negli ultimi anni uno sviluppo crescente. In questo articolo si presentano i risultati ottenuti negli ultimi cinque anni, nella funzionalizzazione selettiva, in condizioni ossidanti, di diverse tipologie di composti organici mediante l'utilizzo di sistemi catalitici supportati su matrici polimeriche basati sul sistema metiltriossorenio/H_2O_2.

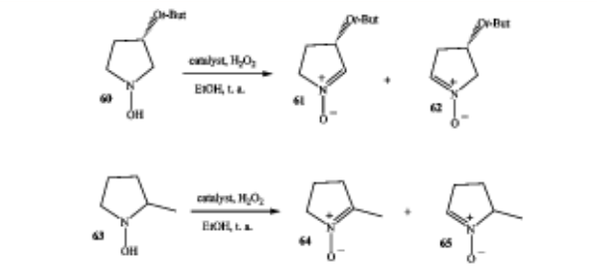
(62%) beside compound 49 (13%) and low amount of isopodophyllotoxone 50 (4%). It is noteworthy that in the case of isopodophyllotoxone derivatives the functionalisation of the C-7 position of the *C*-ring and the ring-opening of the *D*-lactone moiety increased the activity against topoisomerase II while causing the undesired inhibition of tubulin polymerisation to disappear.

Oxidation of *N,N*-disubstituted hydroxylamines to nitrones

Nitrones are very useful building blocks for the synthesis of biologically active nitrogen-containing compounds and, in addition, they are widely used as spin trap reagents in biological systems. Recently, the applicability of polymer/MTO systems to the selective oxidation of a series of hydroxylamines with H_2O_2, including simple acyclic hydroxylamines and *N*-hydroxypyrrolidines, to the corresponding nitrones, has been published. Symmetrically substituted hydroxylamines, and non symmetrical 3-substituted and 2-substituted hydroxypyrrolidines, precursors of nitrones applied in the synthesis of alkaloids and biologically active congeners, have been considered as substrates (Schemes 8 and 9) [8]. Also in this case, the heterogeneous catalysts are shown stable under the reaction conditions with the possibility to be recovered and recycled for at least five times without any appreciable loss in efficiency.



Scheme 8 - Catalytic oxidation of hydroxylamines 52, 54 and N-hydroxypyrrolidines 56, 58



Scheme 9 - Catalytic oxidation of non symmetrical pyrrolidines 60, 63

N,N-diethylhydroxylamine 52, *N,N*-dibenzylhydroxylamine 54, *N*-hydroxypyrrolidine 56, and 3,4-isopropylidenedioxy-*N*-hydroxypyrrolidine 58 were used as representative model compounds of symmetrically substituted acyclic and cyclic hydroxylamines (Scheme 8). In all cases quantitative conversions of the starting materials 52, 54, 56 and 58, which yield the corresponding nitrones 53, 55, 57 and 59 respectively, have been observed with heterogeneous catalysts I-III and V, being the microencapsulated system V the most active catalyst among the heterogeneous compounds used.

According to these data, the coordination of the rhenium atom by pyridine ligands in poly(4-vinylpyridine)/MTO compounds partially decreases the reactivity of the peroxorhenium intermediate toward hydroxylamines, even if the possibility of a concentration process of the substrates inside the low polar microenvironment of polystyrene microcapsules cannot be completely ruled out.

In order to evaluate the regioselectivity of the catalytic oxidative process, the non symmetric hydroxylamines 60 and 63 were successively analyzed (Scheme 9). Under analogous experimental conditions, the oxidation of (*S*)-3-*tert*-butoxy-*N*-hydroxypirrolidine 60 afforded, quantitatively, a mixture of the nitrones 61 and 62, even if with low regioselectivity. A similar outcome was observed with the more electron-rich 2-methyl-*N*-hydroxypirrolidine 63. In this case, besides an astonishing high reactivity showed by the heterogeneous catalytic systems, it must be pointed out that a remarkably high selectivity, compared to the other catalysts used, was obtained in the case of microencapsulated PS-2%/MTO V, being the nitrone 64 the only recovered product of reaction, with no traces of isomer 65.

In conclusion, the results we have reviewed in this article, undoubtedly confirm that the novel polymer supported MTO/H_2O_2 catalytic systems offer a significant contribute in the development of more environment benign catalytic oxidative reactions. Furthermore, the simple procedures used for the immobilization of transition metal compound, open the way for designing novel and more functionalized polymer supported MTO chiral systems.

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